AIDS and the lung in a changing world

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At the beginning of the AIDS epidemic it was clear that the lung of HIV infected patients was the major target for many infections and tumours.[1 2] However, during the first decade of the disease it was shown that the occurrence of several infections might be prevented by the use of prophylaxis, which has a direct but temporary effect,[3] and more recently the use of highly active antiretroviral therapy (HAART) has been shown to have an indirect (immune restoration) but long lasting effect.[4–7] Thus, in a changing world, today we have three different situations.

First situation: HIV infected patients without access to prophylaxis for pulmonary infections and antiretroviral treatment

Unfortunately, this situation applies to the great majority of HIV infected patients in developing countries and, in developed countries, to those without knowledge of their HIV seropositivity or without appropriate follow up.

In this situation the natural history of HIV associated lung disorders is obviously the same as it was at the beginning of the AIDS epidemic. The range of pathogens possibly responsible for respiratory diseases is very wide with a high frequency of acute bronchitis, bacterial pneumonia, *Pneumocystis carinii* pneumonia (PCP), and tuberculosis.[1 8] Similarly, the variety of non-infectious causes of respiratory disease is also very broad[2] with Kaposi's sarcoma, lymphoid interstitial pneumonitis and, to a lesser degree, lymphoma, emphysema,[9] and primary pulmonary hypertension[10]. In contrast, a link between HIV infection and lung cancer,[11] pulmonary embolism, or bronchial hyperreactivity still remains questionable. New clinical entities such as cytomegalovirus induced alveolar haemorrhage,[12] primary pulmonary lymphoma,[13] and rapidly worsening airway obstruction associated with bronchiectasis[14] have recently been reported in HIV infected patients.

The incidence and prevalence of each of these respiratory disorders are strongly related to two factors. The first is the level of immunosuppression—the relative risks for bacterial pneumonia, tuberculosis, PCP, or fungal infections such as cryptococcosis and aspergillosis are clearly related to the gradual decrease in CD4 lymphocyte count. The second factor is the country in which patients live. In Europe and the USA PCP was the most frequent severe lung disease before PCP prophylaxis became available,[15] while in Africa bacterial pneumonia and tuberculosis were the main causes of severe lung disease.[16–19] However, even within the continent of Africa, recent series have shown that the relative frequencies of lung diseases may differ from one country to another. This is particularly true in HIV infected patients with acute pneumonia unresponsive to standard antibiotics and sputum smear negative for acid fast bacilli. Fibreoptic bronchoscopy systematically performed in such patients has shown a high frequency of non-specific interstitial pneumonia (38% of cases), tuberculosis (23%), and cryptococcosis (13%) in Rwanda[20] and, in contrast, a high frequency of tuberculosis (39%), PCP (33%), and Kaposi's sarcoma (9%) in Zimbabwe.[21] Similarly, a recent study in Phnom-Penh using fibreoptic bronchoscopy with bronchoalveolar lavage (BAL) in HIV infected patients with unexplained pneumonia frequently found *Mycobacterium tuberculosis* (33% of cases) but also *P carinii* (25%) and atypical mycobacteria (17%) (S Chan, personal communication, 1998).

Clearly, local studies should be performed in each developing country with a significant number of HIV infected patients to determine the relative frequencies of respiratory diseases. This knowledge will be essential for selecting the most appropriate management algorithm for pneumonia and choosing the most effective prophylaxis.

Second situation: HIV infected patients with access to prophylaxis for pulmonary infections but not to antiretroviral treatment

During the first decade of the AIDS epidemic this situation applied to most of the patients in developed countries and currently it applies to a large number of HIV infected patients in developing countries.

In patients who are not receiving antiretroviral treatment, particularly HAART, the prophylaxis of pulmonary infections remains a major goal because of the high incidence and short term mortality resulting from these infections and because they increase the rate of HIV replication and accelerate the course of the disease.[22 23] In practice, prophylaxis should aim mainly at the prevention of PCP, tuberculosis, and bacterial pneumonia because these three infections together account for at least 80% of severe lung diseases in all countries.[8 15 21]

The USPHS/IDSA guidelines for PCP prophylaxis are clear. Primary prophylaxis is indicated in all cases, including pregnant women, with a CD4 titre of less than 200/mm^3 or a history of oropharyngeal candidiasis. Secondary prophylaxis is indicated in all patients with a prior episode of PCP. Trimethoprim-sulphamethoxazole (TMP-SMZ) is the drug of choice[24] and its effectiveness in the prevention of PCP has been clearly shown in several prospective randomised trials.[25 26] However, one practical problem and one theoretical question still persist about this prophylaxis.

The practical problem is the best strategy to use in patients with TMP-SMZ intolerance.[25 26] Three steps might be proposed according to the severity of the side effects: (1) to continue TMP-SMZ with a decrease in dose or frequency[25]; (2) to withdraw TMP-SMZ and then to reintroduce it in progressively increasing doses (desensitisation) according to published regimens[24]; (3) to switch to another prophylactic drug such as dapsone[25 27] or atovaquone.[27]

The theoretical question deals with the possible consequences of the long term use of TMP-SMZ and, more particularly, the risk of emergence of TMP-SMZ resistant *P carinii*. In a retrospective study Helweg-Larsen *et al*[28] have shown that *P carinii* presents mutations on the impact side of TMP-SMZ in 20% of episodes of PCP. The mutations were significantly more common in patients previously exposed to sulphonamides and, in a multivariate analysis, the presence of these mutations was found to be the most important predictor of death related to PCP. These data suggest that resistance to sulphonamides may result from PCP dihydropteroate synthase gene mutations[29 30] and raise the PCP mortality rate. If this is the case, the theoretical question could become a practical problem.

In the USPHS/IDSA guidelines primary prophylaxis of tuberculosis is indicated in two groups of HIV infected

patients: those in close contact with persons with infectious tuberculosis and those with a positive purified protein derivative (PPD) test. In both groups primary prophylaxis should only be started after active tuberculosis has been excluded by clinical and radiological evaluation. Treatment with isoniazid for 9 months or rifampin (or rifabutin) plus pyrazinamide for 2 months is equally effective. Secondary prophylaxis is not recommended.[24] The effectiveness of isoniazid given for 6 or 12 months as primary prophylaxis has recently been confirmed by a meta-analysis of seven randomised trials, four of which were performed in Africa,[31] which confirmed that isoniazid reduced the risk of tuberculosis in patients with a positive PPD test. However, isoniazid did not reduce the mortality (resulting from HIV infection) in any group of patients.

If tuberculosis prophylaxis is theoretically justified in all patients with a positive PPD test,[32] some practical questions remain to be answered:

- What is the feasibility of the widespread diffusion of such prophylaxis within tuberculosis and AIDS programme conditions in developing countries?[33]
- What is the risk of an increase in tuberculosis resistance to isoniazid and/or rifampin,[34] particularly if prophylaxis is given to patients with active tuberculosis?
- What is the optimal duration of prophylaxis since no prophylaxis is able to eradicate the whole population of *M tuberculosis* or to protect against reinfection?[35]

With regard to the high level of tuberculosis "recurrences" in some developing countries, Fitzgerald *et al* have recently performed a randomised trial of secondary prophylaxis (isoniazid versus placebo) in HIV infected patients after complete cure of tuberculosis and found that isoniazid decreased the risk of recurrence, particularly in HIV infected patients with a history of symptomatic HIV disease before the initial diagnosis of tuberculosis.[36] As in studies of primary prophylaxis, isoniazid alone did not prolong survival,[36] but mortality was reduced when isoniazid was combined with another anti-infectious agent such as sulphadoxine-pyrimethamine.[37]

The USPHS/IDSA guidelines for the prophylaxis of bacterial pneumonia mainly concern pneumococcal disease because of its high frequency and severity. Pneumococcal vaccine is indicated in all patients with a moderate level of immunosuppression and should be given as soon as possible after the diagnosis of HIV infection.[24] These recommendations are based on the result of case-control or observational cohort studies. In a recent retrospective case-control study by Guerrero *et al* pneumococcal vaccine reduced the risk of pneumonia by nearly 70%.[38] In the observational cohort study by Schuchat *et al*[39] a significant reduction in the incidence of invasive as well as non-invasive pneumococcal disease was observed following pneumococcal vaccination, but only in patients with a CD4 cell count of more than 200/mm^3. Finally, in a case-control study Breiman *et al*[40] found that the pneumococcal vaccine prevented invasive pneumococcal disease in 50% of subjects, after adjustment for CD4 cell count, but its effectiveness had not been observed in the subgroup of HIV infected patients of African origin. Because the incidence and recurrence rates of invasive pneumococcal disease are high in Africa,[41] French *et al*[42] evaluated the effectiveness of pneumococcal vaccine in a prospective randomised trial in a cohort of HIV infected Ugandan adults and were surprised to find that the vaccine was ineffective in the prevention of invasive as well as non-invasive pneumococcal diseases including those due to serotypes included in the vaccine. Moreover, the vaccine appeared to increase the risk of developing pneumonia, whatever the cause. French *et al* suggest that this harmful effect of pneumococcal polysaccharides might be due to the destruction of polysaccharide responsive B cell clones.[42 43]

Since the effectiveness and safety of pneumococcal vaccine are questionable, particularly in central Africa, it is logical to consider alternative strategies for protection, mainly chemoprophylaxis.[43] In some prospective or case-control studies of PCP or *Mycobacterium avium intracellulare* (MAC) prophylaxis the use of TMP-SMZ[44 45] or macrolides[46] was associated with a low incidence of bacterial infections.[24] Similarly, in a retrospective cohort study by Buskin *et al*[47] TMP-SMZ lowered the risk of major infections and deaths not attributable to PCP. This beneficial effect has recently been evaluated in two prospective randomised trials in Abidjan (Côte d'Ivoire).[48 49] Anglaret *et al*[48] administered TMP-SMZ to HIV infected patients in clinical stage 2 or 3 of the WHO classification and found a significant decrease in hospital admissions—mainly those due to bacterial pneumonia, malaria, isosporiasis, and acute unexplained fever—at 12 months. Wiktor *et al*[49] administered TMP-SMZ to HIV infected patients with positive tuberculosis tests and found a significant decrease in hospital admissions, mainly those due to septicaemia or enteritis. Moreover, as in the study by Buskin *et al*,[47] there was a significant decrease in mortality, particularly among patients with a low CD4 cell count.[49]

Considering these results and the limits of pneumococcal vaccination,[42] it may be attractive to recommend the use of TMP-SMZ as systematic prophylaxis in all developing countries with a significant number of HIV infected patients. However, before doing so there are four questions to consider:

- Which patients are likely to benefit from TMP-SMZ: those treated for tuberculosis[49] and/or those with any HIV related symptoms[48] and/or those with a CD4 cell count of less than 500/mm^3?
- What is the effectiveness of TMP-SMZ prophylaxis in countries where the percentage of TMP-SMZ resistant bacteria is high?[48]
- What is the effectiveness of TMP-SMZ prophylaxis in countries without malaria?[48]
- What is the long term risk of increasing the resistance of usual bacteria to TMP-SMZ?[24] For example, the frequency of TMP-SMZ resistant bacteria has recently increased in HIV units in San Francisco and this increase coincided with the increase in prophylactic use of TMP-SMZ in HIV infected patients. The frequency of TMP-SMZ resistant bacteria has also increased in non-HIV units and multidrug resistance has been reported.[50]

In many developing countries without access to antiretroviral treatment, prophylaxis could significantly reduce morbidity and mortality in HIV infected patients. Effective regimens exist to prevent PCP, tuberculosis, and bacterial pneumonia. However, each country must determine the most appropriate prophylaxis strategy, taking into account the local spectrum of infections and the local prevalence of resistant pathogens. Whatever the prophylactic programme chosen, it is very important to evaluate periodically the susceptibility of the pathogens to the drugs used.[24]

Third situation: HIV infected patients with access to prophylaxis for pulmonary infections and to HAART

The first and major beneficial effect of HAART is a dramatic reduction in the occurrence of opportunistic infections and, to a lesser degree, of Kaposi's sarcoma.[6 7 51 52] For example, in the French epidemiological database with follow up data on more than 34 000 HIV infected patients in 1998, the incidence of PCP per 10 000 people years decreased from 174 in 1995 to 47 in 1998.[53] During the same period a similar decrease in the incidence

of cytomegalovirus disease, MAC disease, toxoplasmosis, and Kaposi's sarcoma was observed. Interestingly, the remaining opportunistic infections occurred at a high level of immunosuppression whatever the period and, in 1998, they were almost exclusively observed in patients who had not received HAART or in whom it had been ineffective.[53] It is therefore reasonable to try to withdraw the prophylactic treatment of opportunistic infections from patients successfully treated with HAART. Prospective and retrospective studies have shown that the risk associated with the arrest of primary or secondary prophylaxis against PCP appears to be quite low in patients receiving HAART whose CD4 cell counts have risen above 200/mm^3 for 3 or 6 months.[51 54–56] Similar results have been obtained with other opportunistic infections. Specific prophylactic regimens can therefore be safely discontinued in patients in whom CD4 cell counts have increased above the thresholds for initiating prophylaxis.[24 51] Similarly, in cases of delayed HAART failure it seems reasonable to use the same criteria for restarting prophylaxis as for initiating it.[51]

The second beneficial effect of HAART is a reduction in the occurrence of tuberculosis and bacterial pneumonia. However, this reduction is limited, particularly for bacterial pneumonia. In the French epidemiological database the incidence of tuberculosis per 10 000 people years decreased from 84 in 1995 to 36 in 1998 and the incidence of bacterial pneumonia from 279 in 1995 to 192 in 1998.[53] Unlike the other opportunistic infections, bacterial pneumonia and tuberculosis occurred with a lesser degree of immunosuppression in 1998 than in 1995. At this level of immunosuppression *Streptococcus pneumoniae* and *Haemophilus influenzae* were the causal organisms, but not *Pseudomonas*. Clearly, the risk of tuberculosis and/or bacterial pneumonia decreases but still persists in patients successfully treated with HAART. If we remember that acute pneumonia is a major cause of death in HIV infected patients before AIDS stage,[52] the preventive treatment of both infections might be a major goal in this situation. Thus, pneumococcal vaccination or isoniazid prophylaxis might be given to patients on HAART with, respectively, a CD4 cell count reaching 200/mm^3 or with conversion from a negative to a positive PPD test.

Unfortunately, there are some harmful effects of HAART, either directly or indirectly. The first of these is the paradoxical worsening of opportunistic pneumonia after initiation of HAART.[5 52] In a prospective study Narita *et al*[58] examined the incidence of paradoxical responses in patients treated for pulmonary tuberculosis and found a higher incidence (36%) in HIV infected patients receiving antituberculosis treatment and HAART than in HIV negative patients receiving antituberculosis therapy (2%) or in HIV positive patients receiving antituberculous treatment but not HAART (7%). The paradoxical responses were either worsening of initial localisations of tuberculosis or the occurrence of apparently new localisations of tuberculosis in spite of adequate antituberculous treatment. It is noteworthy that these paradoxical responses occurred a long time after the initiation of antituberculous therapy but a short time after the initiation of HAART. In all cases HAART was rapidly successful—as shown by a marked fall in the HIV viral load and conversion from a negative to a positive PPD test—at the time of the paradoxical response. More recently we have described three cases of acute respiratory failure following early introduction of HAART in patients treated for PCP.[59] The three patients had severe PCP that initially improved with anti-PCP and adjunctive steroid treatment but 7–17 days after introduction of HAART they developed a second episode of severe acute respiratory failure with fever and patchy alveolar opacities. Bronchoalveolar lavage and transbronchial biopsy specimens showed severe non-specific pulmonary inflammatory foci surrounding a few persistent *P carinii* cysts. All three patients recovered after stopping HAART and/or reintroducing steroids. These paradoxical responses probably result from the first phase of immunity restoration[60 61] with rapid pulmonary recruitment of fully competent immune and inflammatory cells responding to a few persistent *M tuberculosis* or *P carinii*. Similar immune and inflammatory responses probably contribute to other clinical manifestations of immunologically mediated diseases observed after initiation of HAART.[52] Similarly, Morris *et al*[62] recently reported the case of an HIV infected woman who developed subacute hypersensitivity pneumonitis in response to bird exposure only after a rapid improvement in her CD4 T lymphocyte count secondary to starting HAART.

A second harmful effect of HAART is the emergence of sarcoid like pulmonary disorders. We have recently reported two HIV infected patients with diffuse opacities, thoracic adenopathy, CD4 lymphocytic alveolitis, parotid or salivary gland enlargement, increased serum levels of angiotensin converting enzyme, non-caseating granuloma, and a negative PPD test. These radiological and biological data were noted in patients with undetectable levels of HIV and a CD4 cell count of more than 200/mm^3 as a result of long term HAART in one case and the association of HAART and interleukin (IL)-2 in the other. Antituberculous treatment was unsuccessful. In one case improvement was obtained when IL-2 was withdrawn.[63] Since this first report we have collected six more cases (unpublished). The development of this sarcoid-like process may result from the second phase of immunity restoration which mainly involves the naive and IL-2 receptor positive T cells.[60 61]

Another group of harmful effects of HAART are antiretroviral drug induced respiratory disorders. So far, lactic acidosis with tachypnoea or exercise induced dyspnoea is the most striking side effect reported with these drugs.[63] However, recent communications have reported hypersensitivity reactions to abacavir.[64 65] Respiratory physicians should be particularly aware of these reactions for two principal reasons: (1) a respiratory symptom such as tachypnoea, cough, or pharyngitis associated with fever or rash is present in nearly 20% of hypersensitivity cases; and (2) in cases of rechallenge respiratory symptoms reappear within hours if they were present on the initial reaction. These symptoms are more severe and an adult respiratory distress syndrome (ARDS) associated with hypotension and tachycardia is present in 6% of cases.[64] Moreover, ARDS may lead to death, as reported by Escaut *et al*.[65]

Finally, the interactions between antiretroviral drugs and anti-infectious drugs such as antituberculous agents are indirectly harmful. Rifamycin containing regimens are the most effective in curing tuberculosis in HIV infected patients but rifampin cannot be given with a protease inhibitor or a non-nucleoside inhibitor of reverse transcriptase because of their metabolic interactions.[23 66 67] Clinicians must therefore choose between three options: (1) standard antituberculous therapy without antiretroviral treatment; (2) standard antituberculous therapy with nucleoside inhibitors of reverse transcriptase; or (3) standard antituberculous therapy in which rifabutin at half the dose is substituted for rifampin.[68]

Whatever the harmful effects of HAART, they are considerably less than their beneficial effects. However, one practical problem still remains—namely, the optimal time for introduction of HAART in HIV infected patients with an opportunistic infection. Immediate introduction may avoid the increase in HIV replication and accelerate the cure of infections responding poorly to anti-infectious

agents but delayed introduction may avoid a paradoxical response, a cumulative number of side effects, and some drug interactions. This question remains to be answered.

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